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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 10/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/275,883	RENNER ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *75-78,81-84,86-103,105-107 and 109-145* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) *102* is/are allowed.

6)☐ Claim(s) *75-78,81-84,86-101,103,105-107 and 109-145* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 March 1999* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/4/2000*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

An Appeal Brief was received and entered on 8/9/04.

An appeals conference was held on 10/19/04 at which time the Examiner indicated to the Conferees that claims 137-145 were inadvertently omitted from the enablement rejection. As a result of this error, prosecution is hereby reopened and this rejection is Non-Final.

Claims 75-78, 81-84, 86-103, 105-107, and 109-145 are pending and under consideration in this Office Action.

Information Disclosure Statement

This application has been converted to an electronic file. The electronic file does not contain a copy of the PTO Form 1449 received by the Office on 1/4/00 that is signed and initialed by the Examiner. A signed and initialed copy is included in this Action. The references have been considered.

Drawings

The Drawings stand objected to for the reasons of record in the Notice of Draftsperson's Drawing Review (Form 948) attached to Paper No. 22.

Claim Objections

Claims 75, 103, and 125 and dependents are objected to because they recite "at least one second nucleotide sequence" without ever reciting any first nucleotide sequence. Deletion of the word "second" is suggested.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 96 and 119 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 96 and 119 are indefinite because they recite "said RNA" without proper antecedent basis. Claim 96 depends from claim 94 which provides two different antecedents for "said RNA", i.e. "an untranslated RNA molecule" and "at least one RNA molecule of claim 90". Claim 119 depends from claim 117 which provides two different antecedents for "said RNA", i.e. "an untranslated RNA molecule" and "at least one RNA molecule of claim 113".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 75-78, 81-84, 86-101, 103, 105-107, and 109-145 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention encompasses the genus of DNA molecules comprising an open reading frame encoding a non-cytopathic, temperature-sensitive alphaviral replicase, wherein the non-cytopathicity and temperature-sensitivity are conferred by one or more mutations in the genes encoding the non-structural proteins of the replicase.

Alphaviral replicases are composed of four "non-structural protein" subunits: nsP1, nsP2, nsP3, and nsP4. These proteins are initially expressed as a polyprotein that subsequently undergoes a series of proteolytic processing events to yield the four individual subunits. The function of each these proteins is currently the subject of research. At the time the invention was filed, nsP4 was believed to comprise a polymerase catalytic activity based on homology to known RNA polymerases. See e.g. Shirako et al (J. Virol. 72(3):2310-2315, 3/1998) at page 2310, first sentence of paragraph bridging columns 1 and 2. NsP1 was thought to encode a methyltransferase and was known to be required for initiation of minus strand RNA synthesis. The function of nsP3 was undefined at the time of the invention. See e.g. Suopanki et al (J. Gen. Virol. (79:309-319, 1998) paragraph bridging pages 309 and 310. The nsP2 subunit was known to regulate RNA synthesis, to contain an N-terminal helicase motif, and to contain a C-terminal proteinase that processes the polyprotein. See Dryga et al (Virology 228: 74-83, 1997).

The Office has acknowledged that a variety of temperature sensitive alphaviral replicase mutations were known in the art at the time of the invention. However, at the time of the invention, only a single mutation conferring a non-cytopathic phenotype on

an alphaviral replicase was known, i.e. P726S of nsP2, characterized by Dryga (1997). The central issue in this analysis is whether the specification has disclosed a number of species that is representative of the claimed genus of mutations that confer the non-cytopathic phenotype. Applicant is referred to the interim guidelines on written description published December 21, 1999 in the Federal Register, Volume 64 Number 244, pp. 71427-71440 (also available at www.uspto.gov). The following passage is particularly relevant.

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.
>
> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within a genus, one must describe a sufficient number of species to reflect the variation within the genus. What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus.

The specification discloses no mutation, other than P726S, that renders an alphaviral replicase non-cytopathic. While the prior art taught a variety of temperature sensitive mutations that allow cellular growth at permissive temperatures, these are not considered to be non-cytopathic mutations within the context of the invention because the replicases carrying these mutations are cytopathic at the non-permissive temperature.

The specification and the prior art of record provide no guidance whatsoever as to what types of mutations, other than P726S, will cause a non-cytopathic phenotype,

and no guidance as to what replicase structure is required for a non-cytopathic phenotype. As such, one of skill in the art at the time of the invention had no framework from which to base a rational approach to constructing other non-cytopathic mutants. For example, it was known that P726 is located in the C-terminal portion of nsP2, downstream of a region that comprises the nsP polyprotein protease, but Dryga (1997) showed that the P726S mutation does not affect the kinetics of proteolytic processing of the non-structural proteins, which is the only function this portion of nsP2 was known to have at the time of filing. See page 79, column 1, first full paragraph. Dryga also taught that the mutation had no significant effect on RNA synthesis. See paragraph bridging pages 78 and 79. There is no evidence of record of any effect of P726S on the nsP helicase activity, or on any other activity of the replicase. In fact, neither the specification nor the prior art of record provides any guidance as to why P726S causes a reduction in cytopathicity, or what replicase structure is required for non-cytopathicity. So, one of skill in the art at the time of the invention had no theoretical basis for attempting to replicate the effect of the P726S mutation with other mutations, because the mechanism of reduced cytopathicity, the replicase structure required for non-cytopathicity, and the role of P726S in that mechanism and structure, were unknown at the time of filing and the specification provides no guidance in this regard. Subsequent to the time of the invention, Frolov et al (J. Virol. 73(5):3854-3865, 1999) identified a second non-cytopathic mutation at position 779 of nsP2 (i.e. N779K), but stated that the function of the region in which P726 and N779 occur was unknown. See first sentence of paragraph bridging pages 3862 and 3863. So, there

could be no correlation between the structure of the P726 region and the function of that region, because the function of that region remained unknown even after the time of filing.

As shown above, the state of the art of the prediction of replicase cytopathicity function based on replicase structure is not sufficiently advanced to predict *a priori* what mutations will confer non-cytopathicity on a given alphaviral replicase, so it falls to the specification to provide this information. One of skill in the art appreciates that a wide variety of alphaviral replicases is known in the art, see e.g. instant claims 128-130 which list 22 different alphaviruses. In view of this recognized variety, and in view of the uncertainty associated with predicting which amino acid substitutions will confer non-cytopathicity on a given polymerase, the disclosure of only a single species is considered insufficient to convey to one of skill in the art that applicant was in possession of the claimed genus at the time of the invention.

The courts have found that merely describing the functional characteristics of a protein encoded by a particular nucleic acid is insufficient to adequately describe the genus of nucleic acids encoding that protein. A gene is a chemical compound, albeit a complex one, and it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it. See Oka, 849 F.2d at 583, 7 USPQ2d at 1171. Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to

define it solely by its principal biological property, e.g., non-cytopathic, temperature-sensitive alphaviral replicase, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. When an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, conception has not been achieved until reduction to practice has occurred, i.e., until after the gene has been isolated. Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016, 1021 (Fed. Cir. 1991). The instant application does not provide a written description that would allow one of skill in the art to immediately envisage the specific structure for Sindbis virus non-cytopathic, temperature-sensitive replicase, or for the broader genus of alphaviral non-cytopathic, temperature-sensitive replicase. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed* (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116). As there is disclosure of only a single species of the claimed genus of polynucleotides, and the art is unpredictable, the skilled artisan cannot envision the detailed chemical structure of any other species of the claimed genus, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of

isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

The limited information provided in the specification is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of the broadly claimed polynucleotides at the time the application was filed. Thus it is concluded that the written description provision of 35 U.S.C 112, first paragraph, is not satisfied for the claimed polynucleotides. Applicants are reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C 112 is severable from its enablement provision (see page 1115).

Response to Arguments

Applicant's arguments filed 8/9/04 have been fully considered as they apply to the rejection above but they are not persuasive. Applicant considers the issue of written description at pages 12-25 of the response. As noted above, the central issue for consideration is whether or not the specification has described a representative number of species of the claimed invention. The specification has described only a single specie by complete structure and reduction to practice. Because the genus embraces any nucleic acid encoding any temperature sensitive and non-cytopathic alphaviral replicase, and because the art of protein structure/function relationships of non-cytopathic alphaviral replicases is unpredictable, description of additional species by relevant identifying characteristic is warranted. Applicant argues at pages 14-17 and

22-25 of the response that the structural and functional characteristics of the claimed nucleic acids are described adequately to satisfy the requirements of 35 USC 112 first paragraph regarding relevant identifying characteristics. The basis of this argument is that the specification discloses that 1) the nucleic acids must encode a non-cytopathic alphaviral replicase (function), and that 2) this function is bestowed by one or more mutations in the genes encoding non-structural proteins of the alphavirus (structure). However, even the narrowest of the rejected claims only limits the structure of the nucleic acids only by limiting the identity of the replicase subunit in which the mutations must occur. There are no limitations whatsoever on where in any subunit the mutations must occur, or what type of mutation is required to yield the desired function. Because of the unpredictable nature of the effects of amino acid substitutions on replicase function, established above, one of skill in the art would not consider the mere identification of a subunit which is to be mutated as a relevant identifying characteristic of a type of mutation, e.g. a mutation rendering an alphaviral replicase non-cytopathic. Instead, the description requirement could be satisfied by the identification of specific amino acid positions of a protein at which the required types of mutations can be made, a description of the types of amino acid substitutions that can be used to obtain the desired function, or the structural characteristics that yield the desired function, such that one of skill in the art would be convinced of some correlation between structure and function. The specification fails to supply such information, other than the single example of the P726S nsP2 species.

The Office has acknowledged that a variety of temperature sensitive alphaviral

replicase mutations were known in the art at the time of the invention. However, at the time of the invention, only a single mutation conferring a non-cytopathic phenotype on an alphaviral replicase was known, i.e. P726S of nsP2. It is noted that at pages 15-16 of the response, Applicant cites portions of the specification that might lead one to believe otherwise. This passages cite the Weiss (1980) and Dryga (1997) publications. However, these publication disclose only the nsP2 P726S mutation, consequently the specification discloses only a single example of a single mutation conferring a non-cytopathic phenotype on an alphaviral replicase, a single example of an alphaviral replicase that is both temperature sensitive and noncytopathic, and no examples at all of an alphaviral replicase in which the required functional characteristics are cause by only a single mutation, such as is embraced by the claims. If the Examiner is incorrect on this point, Applicant is urged to point to the precise passage in the specification, or to the prior art publication, that discloses a replicase mutation, other than P726S, that causes a non-cytopathic phenotype.

At pages 17-19 Applicant argues that there is a known correlation between non-cytopathic function and mutational structure. In the last sentence of page 17 Applicant indicates that there are numerous examples of mutations in alphaviral replicases that cause a non-cytopathic effect. Applicant then lists twelve publications, one of which discloses the P726S mutation, i.e. Dryga (1997). Applicant concludes that it was recognized in the art that non-cytopathicity was conferred by mutations in the nsP genes of alphaviral replicases. This is unpersuasive because only one non-cytopathic mutation was disclosed in these publications. If the Examiner is incorrect on this point,

then Applicant is urged to point to the other non-cytopathic mutations. The disclosure of only a single mutation, P726S, simply cannot provide a correlation between structure and function that would convey to one of skill in the art that Applicant was in possession of the claimed genus, because the function of the nsP2 region in which P726 occurs is unknown, and the structural requirements for a non-cytopathic replicase, other than a P726S mutation, were unknown. See Frolov et al (1999), first sentence of paragraph bridging pages 3862 and 3863. The absence of such a correlation is also clear from the teachings of Dryga (1997) who posits no explanation for the effect of the mutation on the function of the protein, and who shows objectively that the mutation has no effect on the protease activity of the protein, even though it occurs close to the protease domain. Neither the specification nor the prior art teach what it is about the structure of the P726S mutation that leads to non-cytopathicity, or how one might obtain that structure with any other mutation.

Applicant goes on to state that one could have easily obtained further mutations, relying for support on the Declaration of Dr. Schlesinger filed 3/31/2003, and considered in the Office Action of 6/17/03. The Declaration of Dr. Schlesinger is a statement of opinion regarding the feasibility of obtaining mutants through screening, and has no bearing on the issues of what was described in the specification or what Applicant was in possession of at the time of the invention. Applicant is reminded that the description and enablement requirements are distinct, so the contention that mutations are easily made does not address the issue of whether or not they have been adequately described.

At pages 19 and 20 of the response Applicant argues that the mutations disclosed in the specification would have directed persons of ordinary skill in the art to additional non-cytopathic mutations in other alphaviruses. The Office agrees that one of ordinary skill in the art could identify in other alphaviral nsP2 proteins a residue corresponding to Sindbis virus P726, and that it is likely that a P276S mutation would have a non-cytopathic effect in these viruses. However, the specification fails to identify any other mutation that confers the required phenotype, and provides no relevant identifying characteristic of such a mutation, such as a significant correlation between any structure and any function, as discussed above. As such, the argument is unpersuasive.

At page 21 of the response, Applicant argues that the written description requirement is satisfied for claims that require that the non-cytopathic mutation must occur in nsP2. This argument is unpersuasive for the reasons set forth above, i.e. the specification discloses only a single species of the claimed genus, and fails to provide any relevant identifying characteristic that would convey to one of skill in the art that Applicant was in possession of the claimed genus. The specification provides no correlation between the structure of nsP2 and its function in the required non-cytopathic phenotype, and provides no guidance as to what mutation, other than P726S, will result in the required phenotype.

At pages 22-25 of the response, Applicant argues that the Examiner has failed to establish a prima facie case of lack of written description. Applicant argues that the description requirement does not necessarily require disclosure of multiple working

examples or disclosure of all mutations that render alphaviral replicases non-cytopathic. The Office agrees and notes that in situations were the invention is not reduced to practice or complete structural description, the requirement may be satisfied by description of a representative number of species or relevant identifying characteristics of the claimed genus. As discussed above, the specification fails to provide such a disclosure. At page 23, Applicant argues that one of ordinary skill in the art could have used the instant disclosure to obtain the claimed mutants. This is unpersuasive because the issue under written description is not whether one can make the claimed invention, but rather whether it has been adequately described. Applicant is reminded that the written description and enablement requirements are severable. See *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d.

Applicant argues that the Examiner has failed to point to any legal authority to support a requirement that one must be able to envisage the sequence of every nucleic acid molecule encompassed by the instant claims. This is because the Examiner has not required such. The Examiner has clearly stated that what is required is description of a representative number of species of the claimed genus, either by reduction to practice or by description of relevant identifying characteristics, such as a correlation between structure and function. The specification fails to provide such a description for the reasons given above. Applicant argues that the Examiner relies improperly for support on cases such as *Amgen* and *Fiers v Revel* because these cases involve claims or counts that defined the invention by functional language only. This is unpersuasive because the rejected claims provide no substantial structural requirement

either. Instead, the narrowest of the rejected claims requires a nucleic acid encoding an alphaviral replicase in which non-cytopathicity is conferred by one or more mutations in the nsP2 subunit of the replicase. These claims have no requirement as to where in the nsP2 sequence the mutation(s) should occur, and no requirement as to what amino acids may be substituted, deleted, or added. The prior art disclosed many nsP2 mutations, and only one was identified as noncytopathic (i.e. P726S). See e.g. Shirako et al (Virology 177: 54-64, 1990) and Hardy et al (Virology 177: 199-208, 1990) who disclose 3 (see Fig. 1A at page 57) and 5 (see paragraph bridging pages 201 and 202) nsP2 non-cytopathic mutations, respectively. At the time of the invention, out of all of the mutations known to occur in alphaviruses, only one caused a non-cytopathic phenotype. Because the vast majority of known mutations in alphaviruses, including in the nsP2 subunit, are not non-cytopathic, one of skill in the art would require some description of the region in which mutations can be made to achieve non-cytopathicity, and what type of mutations should be made in that region. The specification fails to provide such a description.

It has been established by the Office that the state of the art of alphaviral replicase protein structure and function is highly unpredictable, particularly with respect to the effects of mutations that cause a non-cytopathic phenotype. At the time the invention was filed, the art provided no guidance as to what replicase structure was required for non-cytopathicity, or as to why the single known non-cytopathic mutation caused a non-cytopathic phenotype. The guidelines on written description published December 21, 1999 in the Federal Register, Volume 64 Number 244, pp. 71427-71440

(also available at www.uspto.gov) state:

> In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus.

Additionally, the courts in *In re Shokal*, 113 USPQ 283 (CCPA 1957) found that

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

The claimed genuses embrace mutations in any of four structurally distinct genes in any known alphavirus. The claims are supported by a description of only a single species. Therefore, one of skill in the art could not conclude that Applicant was in possession of the claimed genus at the time the invention was filed.

For these reasons the rejection is maintained.

Enablement

Claims 75-79, 81-84, 86-101, 103, 105-107, and 109-145 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a DNA molecule encoding a non-cytopathic, temperature-sensitive alphaviral replicase with a P726S nsP2 mutation conferring a non-cytopathic phenotype, does not reasonably provide enablement for DNA molecules encoding any other alphaviral non-cytopathic, temperature-sensitive alphaviral replicase. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The claims encompass nucleic acid molecules encoding a non-cytopathic, temperature-sensitive alphaviral replicase, methods of using the nucleic acids, alphaviral particles comprising the nucleic acids, and cells comprising the nucleic acids. The molecules encode an open reading frame which must undergo at least one RNA-dependent RNA polymerase-mediated replication event in order to be translatable.

The prior art taught several alphavirus polymerases that are temperature sensitive. However, as discussed above, the prior art taught the existence of a only one alphaviral non-structural protein mutation that conferred a non-cytopathic phenotype, i.e. nsP2 P726S. Neither the specification nor the prior- or post-filing art of record disclose any mutation of a non-structural protein other than nsp2 that conferred a non-cytopathic phenotype.

The specification provides no guidance whatsoever as to what types of mutations of any alphaviral nsP, other than P726S, will cause a non-cytopathic phenotype, and provides no framework from which one of skill in the art could base a rational approach to constructing such mutants. The specification teaches no methods of making or selecting for such mutants. The prior art teaches a single example that succeeded in isolating a single viral isolate (Weiss et al (1980)). The identity of the causative mutation in Weiss (nsP2 P726S) was not determined until 1997. As a result, it is clear that it was not routine in the art at the time of the invention to isolate nsP mutations conferring a non-cytopathic phenotype.

At the time the invention was filed, the prior art provided inadequate guidance such that one of skill in the art had no basis for predicting what mutations would cause non-cytopathicity. For example, it was unknown at the time of filing why P726S caused a non-cytopathic phenotype. This mutation occurs in the C-terminal portion of nsP2 that comprises the nsP polyprotein protease. However, Dryga (1997) showed that it does not affect the kinetics of proteolytic processing of the non-structural proteins, which is the only function this portion of nsP2 was known to have at the time of filing. See page 79, column 1, first full paragraph. Dryga also taught that the mutation had no significant effect on RNA synthesis. See paragraph bridging pages 78 and 79. There is no evidence of record of any effect of this mutation on the nsP helicase activity, or on any other activity of the replicase. In fact, neither the specification nor the prior art of record provides any speculation as to why P726S causes a reduction in cytopathicity. As a result, one of skill in the art at the time of the invention, had no theoretical basis for attempting to replicate the effect of the P726S mutation with other mutations, because the mechanism of reduced cytopathicity, and the role of P726S in that mechanism, were unknown at the time of filing and the specification provides no guidance in that regard. After the filing date of the instant invention Perri et al (2000) isolated five new mutations of Sindbis or Semliki virus nsP2 genes that conferred a non-cytopathic phenotype, but stated that "[i]t remains to be determined whether mutation of other alphavirus nsPs or nsP2 domains can provide a noncytopathic phenotype by a similar or alternative mechanism." See page 9802, column 2, lines 5-8. Further evidence supporting the unpredictability of obtaining non-cytopathic mutants comes from the post-filing art in

Frolov et al (J. Virol. 73(5):3854-3865, 1999) who identified a non-cytopathic mutation at an independent site, i.e. N779K, but stated that the function of the region in which P726 and N779 occur is unknown. See first sentence of paragraph bridging pages 3862 and 3863. So it is clear that there was no basis for rational mutagenesis of this region for the production of non-cytopathic mutations at the time of the invention.

One might argue that it would not be undue experimentation to perform random mutagenesis and to express and assay each construct individually and thereby determine empirically which ones encoded polymerases of the desired phenotype. However, as set forth in In re Fisher, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that scope of claims must bear a reasonable correlation to scope of enablement provided by the specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement varies inversely with degree of unpredictability of factors involved.

In this case, the art is not sufficiently advanced to allow the prediction of mutations that will cause non-cytopathicity, and it was not routine in the art at the time of the invention to obtain such mutants through random mutagenesis or genetic screening. Furthermore, the specification teaches no method for isolating such mutations. While Applicant is not required to disclose that which is well known in the art, there is an obligation to disclose critical elements of the invention as well as how to use these elements. In Genentech, Inc, v Novo Nordisk A/S, the court found that when the specification omits any specific starting material required to practice an invention, or the

conditions under which a process can be carried out, there is a failure to meet the enablement requirement. See 42 USPQ2d 1001.

> It is true, as Genentech argues, that a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

In this case, the method of making non-cytopathic mutations other than nsP2 P726S is a critical aspect is not a minor detail that can be omitted in the process of providing an enabling disclosure. In view of the fact that only one non-cytopathic mutation was known at the time of the invention, the production of such mutations was clearly not routine in the art, and the it falls to the specification to provide guidance in this regard. Such guidance is absent.

In view of the unpredictability of alphaviral replicase structure-function relationships, the failure of the specification to disclose more than one example of a noncytopathic alphavirus replicase, the failure of the specification to provide any guidance as to what mutations other than nsP2 P726S will provide a non-cytopathic replicase, the unpredictable state of the art regarding what exactly causes the non-cytopathic phenotype attributed to P726S, the failure of the specification to teach how to make non-cytopathic mutations other than P726S, and the fact that non-cytopathic alphaviral replicases were not routinely isolated at the time of the invention, one of skill

in the art could not make the invention commensurate in scope with the claims.

Response to Arguments

Applicant's arguments filed 8/9/04 Applicant argues that have been fully considered as they apply to the rejection above but they are not persuasive.

Applicant argues at pages 28 and 29 that one of skill in the art at the time of the invention could have made mutations in the nsP genes of other alphaviruses that correspond to the nsP mutations described in the instant specification. The Office agrees that based upon the high degree of homology present among alphaviral replicases, one of skill in the art could likely have made mutations in other alphaviral replicases corresponding to Sindbis virus P726S. The problem is that the specification discloses only one non-cytopathic mutant (P726S), and does not reasonably enable the construction of any others for the reasons discussed above.

At pages 29-31, Applicant argues that one of skill in the art could make non-cytopathic mutations without undue experimentation by random mutagenesis and screening. Applicant argues that Weiss (1980) used genetic selection to isolate the P726S mutation, notes that the Declaration of Dr. Schlesinger supports genetic screening as routine, and notes that the Federal Circuit has found that screening large numbers of isolates is not deemed undue experimentation when those of skill in the art typically engage in such screening. This argument is unpersuasive. When one considers the teachings of the specification and the prior art as a whole, it is apparent that those of skill in the art did not routinely screen for non-cytopathic alphaviral

mutations. The prior art of record and the specification together disclose only a single example of such screening, and the recovery of only a single mutation. This is in contrast with, e.g. the production of an antibody against a protein, a process that is routinely carried out such that there is a multitude of examples in the art. As a result, antibodies against adequately described and enabled proteins are considered to be adequately described and enabled as well. The disclosure of only a single instance of the use of genetic screening for non-cytopathic viruses does not support the position that such screening was routine in the art at the time of the invention. Applicant asserts that the Declaration of Dr. Schlesinger supports the use of random mutagenesis and screening for this purpose. However, as discussed previously, the court has found that although a declaration is considered to be evidence itself that must be considered, the weight to give a declaration will depend upon the amount of factual evidence the declaration contains to support the conclusion of enablement. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991) ("expert's opinion on the ultimate legal conclusion must be supported by something more than a conclusory statement"). In this case the Declaration provides no factual evidence whatsoever, and is only a statement of Declarant's beliefs. As such it is insufficient to overcome the prima facie case established by the Office.

At pages 32 Applicant argues that several temperature sensitive mutations were known at the time of the invention, and at pages 37, 38, 42, and 44, Applicant argues that one of skill in the art could have combined temperature sensitive mutations with cytopathic mutations and obtained the predicted temperature sensitive and cytopathic

phenotype. Applicant relies for support on Lundstrom et al (2001) and Lundstrom (2003). The Office is persuaded that one of skill in the art could combine a given temperature sensitive mutation with a given non-cytopathic mutation to likely obtain a replicase that is both temperature sensitive and non-cytopathic, and the statement of the rejection now reflects this. Note that, at the time of the invention, there was only one "given" non-cytopathic mutation, nsP2 P726S, and that the specification fails to teach how to make others without undue experimentation.

At pages 32-36 and 43, Applicant argues that one of skill in the art could have used methods that were available in the prior art to obtain non-cytopathic alphaviral replicase mutants without undue experimentation. Applicant relies first upon the publications of Weiss(1988) and Dryga (1997) who isolated and characterized, respectively the P726S mutation. The Office has stated the scope of claimed replicases comprising this mutation are enabled. Applicant also relies upon the post filing art (Agapov (1998) and Perri (2000)) to support an argument that methods available at the time of filing could have been used in order to produce mutations yielding non-cytopathic alphaviral replicases. Agapov (1998) modified alphaviral replicons to express the dominant selectable marker puromycin acetyltransferase (PAC), and selected for infected cells that could survive puromycin treatment. Agapov recovered a single P726L mutation with a phenotype of reduced cytopathicity. Perri (2000) used a similar selection system that relied upon neomycin resistance instead of puromycin resistance. Perri also performed random mutagenesis in combination with the selection system. Perri recovered two Sindbis virus mutations in nsP2 (A1E and P726T) and

three Semliki Forest virus mutations in nsP2 (L10T, ΔD469, and L713P) that conferred reduced cytopathicity. Applicant's argument is unpersuasive because the methods used by Agapov and Perri were not in use by those of skill in the art at the time of the invention. Applicant argues otherwise, stating that Xiong et al (1989) taught an alphaviral replicon expressing a selectable marker. This is unpersuasive because Xiong did not teach a selectable marker, Xiong taught a reporter gene, i.e. chloramphenicol acetyltransferase (CAT). It is noted that CAT is a bacteriostatic compound used as a selectable marker in bacteria, or more frequently in the non-selective process of amplifying plasmids in bacteria. It is not a selectable marker in eukaryotic cells. It functions by binding to the bacterial 50S ribosomal subunit, which is not present in eukaryotic cells. Xiong worked with eukaryotic cells, not prokaryotic cells, and did not select for cells expressing resistance to chloramphenicol. Instead Xiong assayed for the presence of the CAT protein. Furthermore, Xiong did not use the cited vector to screen for mutations. As a result, Xiong did not teach a method whereby one could select for mutations based on drug resistance, as did Agapov and Perri, and Xiong does not serve as evidence that those of skill in the art routinely used such methods for screening for non-cytopathic mutations at the time the invention was filed.

At pages 39 and 40, Applicant argues that claims requiring that the non-cytopathic mutation must occur in nsP2 are enabled. Essentially, the argument is that limitation to nsP2 provides an adequate structure/function relationship, even though the nature of the mutation is not limited. This argument is unpersuasive for the reasons set forth above, i.e. the unpredictability of nsP2 structure-function relationships, the failure

of the specification to disclose more than one example of a noncytopathic nsP2 mutation, the failure of the specification to provide any guidance as to what nsP2 mutations other than P726S will provide a non-cytopathic replicase, and the unpredictable state of the art regarding what exactly causes the non-cytopathic phenotype attributed to P726S, and the fact that non-cytopathic nsP2 mutations were not routinely isolated by any means at the time of the invention.

At pages 40-41, Applicant argues that one of skill in the art need not be able to predict the effects of mutations on alphaviral replicases because one could use genetic screening approaches and select for noncytopathic replicases. This is unpersuasive because, as discussed above, random screening for noncytopathic replicases was not routine at the time of the invention, and absent guidance concerning where in any nsP to make mutations, or what types of mutations to make, such approaches constitute undue experimentation.

At page 44, Applicant concludes that a prima facie case of lack of enablement has not been established because insufficient evidence or scientific reasoning has been presented to demonstrate the need for undue experimentation. This is unpersuasive because the specification provides no guidance as to how to make any non-cytopathic alphaviral replicase mutation other than P726S, no guidance as to where to make the mutations or what substitution to select, the specification provides no basis for any rational approach to mutagenesis, and fails to enable random screening methods because 1) it teaches none, and 2) such methods were not used routinely to isolate non-cytopathic replicase mutants at the time of the invention. Furthermore, the Office

has demonstrated that it is unpredictable as to what mutations or structures in an alphaviral nsP will give rise to a non-cytopathic replicase, and that neither the prior art nor the specification establishes what structure or what mutations, other than P726S, will do so. This information is required to practice the invention without undue experimentation. Because the specification fails to teach this critical information that is missing from the prior art, one of skill in the art would have had to perform undue experimentation in order to make the invention commensurate in scope with the claims.

Conclusion

Claim 102 is allowable.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, John Leguyader, be reached at 571-272-0760. The official central fax number is 703-872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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